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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/914,046

10/01/2001

Liang Xu

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04/16/2008

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EXAMINER

DIBRINO, MARIANNE NMN

ART UNIT

PAPER NUMBER

1644

MAIL DATE

DELIVERY MODE

04/16/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/914,046	Applicant(s) XU ET AL.	
	Examiner DiBrino Marianne	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4,7,8,12,69,73 and 75-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 73 is/are rejected.
- 7) ☒ Claim(s) 1-4,7,8,12,69 and 75-80 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/25/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment filed 1/25/08 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group II, and species of immunoliposome comprising a pre-linked antibody fragment that binds a transferrin receptor and further comprises DNA encoding wild type p53 in Applicant's responses filed 8/27/04 and 4/30/04. Group I had been rejoined to Group II.

Claims 1-4, 7, 8, 12, 69, 73, 75, 76 and newly added claims 77-80 are currently being examined.

3. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 7, 8, 12, 69, 73 and 75-80 is deemed to be the filing date of PCT US00/04392, *i.e.*, 2/22/00, as the parent provisional application 60/121,133 does not support the claimed limitations of the instant application. The said limitations are those of the ratios recited at the last 3 lines of claim 1 and "MPB" in claim 8.

4. In view of Applicant's amendment of instant claim 1 to delete the recitation of "1:5" and to add in its place the recitation of "1:10" as the lower value in the protein:lipid (w:w) ratio presented in Applicant's amendment filed 1/25/08, the prior 103(a) rejections of record over claims 1-4, 7, 8, 12, 69 and 75-80 are hereby WITHDRAWN.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claim 73 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,248,721 B1 in view of Yu *et al* (Oncogene 11: 1383-1388, 1995, of record), US 2001/0008759 A1 (of record), US 6,448,390 B1, Wright and Huang (Biochim. Biophys. Acta. 1992, 1103: 172-178, of record) and Morishige *et al* (Biochim. Biophys. Acta. 1993, 1151: 59-68, of record).

Claim 73 was previously rejected upon the basis set forth below.

US 6,248,721 B1 discloses that cationic liposomes have proven to be a safe and effective means for inducing the transient expression of DNA in target cells.

US 6,248,721 B1 discloses that cationic liposomes, such as for example DOTAP/DOPE, and ligand targeted cationic liposomes are employed for the delivery of plasmid-DNA encoding a protein(s), the ligand-targeted liposomes made by covalently attaching ligands or antibodies to the surface of the cationic liposome. US 6,248,721

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B1 discloses using monoclonal antibodies such as mAb HMSA5 against melanoma-specific surface antigens when melanoma tumor cells are to be targeted. US 6,248,721 B1 discloses that the DNA is formed into a complex with the preformed cationic liposomes using standard methodology or alternatively the DNA is encapsulated into the liposome interior. US 6,248,721 B1 discloses that the DNA containing liposomes are then used to transfer the DNA to tumor cells *in vivo* by direct intra-tumor injection or *in vitro* (using freshly explanted tumor cells) followed by return of the transduced cells to the recipient (column 50 at lines 9-40).

US 6,248,721 B1 does not disclose making the nucleic acid-cationic immunoliposome recited in instant claim 73 by directly conjugating a scFv antibody fragment such as an anti-Her2/neu scFv antibody fragment to a cationic liposome wherein said antibody fragment is directly conjugated to said liposome via a sulfur atom that was part of a sulfhydryl group at the carboxy terminus on said antibody fragment prior to the formation of the immunoliposome complex.

Yu *et al* teach that cationic liposome-mediated E1A (*i.e.*, a tumor suppressor) gene (DNA) transfer, *i.e.*, in a pharmaceutical composition, significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice. Yu *et al* further teach using a DNA: liposome ratio of 1:13, a ratio that is within the range that is recited in instant claim 1. Yu *et al* teach making cationic liposomes that can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor (especially abstract, page 1385 at column 1 at the first full paragraph, page 1387 at column 1 at the first full paragraph). With regard to the order of the method steps recited in claim 1, Yu *et al* teach addition of the antibody to the liposome, not to the liposome:DNA complex. Yu *et al* teach that the cationic liposome consists of DC-cholesterol and DOPE present at a 3:2 ratio (page 1385 at the first full paragraph).

US 2001/0008759 A1 discloses targeting of ErbB2 (*i.e.*, HER-2/neu)-overexpressing cells has been accomplished primarily using anti-ErbB2 antibodies in different formats, including conjugation to liposomes containing chemotherapeutics ([0004]).

US 2001/0008759 A1 discloses that for liposomal targeting, antibodies should be used that bind specific epitopes and that are subsequently rapidly internalized and yield a functional targeting vehicle ([0005]). US 2001/0008759 A1 discloses that preferred antibodies include scFv antibodies ([0020]). US 2001/0008759 A1 discloses that to facilitate coupling of the purified scFv to liposomes, the C6.5 gene (anti-c-ErbB2 or anti-HER-2/neu scFv) was subcloned into an *E. coli* expression vector resulting in addition of a free cysteine residue at the C-terminus of the scFv, *i.e.*, the said free cysteine residue contains a sulfhydryl group at the carboxy terminus of the antibody fragment, and that use of the immunoliposomes with the scFv targeting antibodies *in vivo* was more effective than use of untargeted liposomes ([0206]).

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US 6,448,390 B1 discloses cationic liposomes such as DOTAP/DOPC/DOPE containing MPB-PE can be directly conjugated to thiolated protein(s), *i.e.*, conjugation occurs via a sulfur atom which was part of a sulfhydryl group at the carboxy terminus of the protein prior to said conjugation (especially Example 13). US 6,448,390 B1 further teaches scFv antibodies, and their use in a chimeric protein as a delivery vehicle (column 21 at lines 2-13).

Wright and Huang teach that MPB-PE was effective at stabilizing the bilayer phase of DOPE in liposomes. Wright and Huang teach that antibody can be attached to liposomes through covalent or non-covalent attachment to derivatized membrane phospholipids such as conjugation of thiolated antibody to preformed liposomes containing MPB-PE, and that such method facilitates proper orientation of the antibody and avoids the use of detergent that is employed with acylated antibody. Wright and Huang teach that conjugation of antibody to PE-based liposomes using this strategy may produce target sensitive immunoliposomes (especially abstract, first full paragraph on page 173 at column 1).

Morishige *et al* teach conjugating Fab' fragments with liposomes containing MPB-PE (PC:Cholesterol:MPB-PE in 10:10:1 molar ratio), and mixing 1 mg Fab' per 6 umol of PC (*i.e.*, 1 mg Fab' with 7,475.4 ug of liposome lipid (or a 1:7.5 ratio of antibody fragment to lipid on a weight:weight basis). Morishige *et al* teach that although they prepared immunoliposomes with two antibodies, there is no experimental evidence that the 2-step targeted immunoliposome is more effective *in vivo* than the conventional 1-step immunoliposome, and that an advantage of using the 2-step system is that if the first antibody is available in purified form, one does not have to purify the second antibody that is the targeting antibody (especially abstract, materials and methods at the paragraph spanning columns 1-2 on page 6, paragraph spanning columns 1-2 on page 61, paragraph spanning pages 66-67).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a cationic immunoliposome comprising DOTAP as disclosed by US 6,248,721 B1 and further comprising MBP-PE as disclosed for the cationic liposome of US 5,448,390 B1 and to have directly conjugated an scFV antibody fragment to said cationic liposome, the said scFv having a carboxy-terminal cysteine and specificity of anti-HER-2/neu disclosed by US 2001/0008759 A1, the MBP-PE stabilizing the bilayer phase of DOPE as taught by Wright and Huang and the ratio of scFV-cysteine antibody fragment to lipid determined on a weight to weight basis for the scFV-cysteine based upon its molecular weight as compared to that of the Fab' fragment used by Morishige *et al* in creating their targeted liposome containing MPB-PE, and further to have incorporated DNA for delivery to tumor cells as disclosed by US 6,248,721 B1 at the ratio taught by Yu *et al*, including for DNA encoding a tumor suppressor gene such as E1A taught by Yu *et al*.

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One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a targeted cationic liposome containing a DNA therapeutic agent capable of targeting said immunoliposome to a Her 2/neu expressing tumor and delivering a tumor suppressor gene to said tumor because:

(1) US 6,248,721 B1 discloses that cationic liposomes, including for instance ones comprising DOTAP/DOPE, have proven to be a safe and effective means for inducing the transient expression of DNA in target cells, that the ligand-targeted liposomes are made by covalently attaching ligands or antibodies, such as with specificity for a tumor antigen, to the surface of the cationic liposome, that DNA may be formed into a complex with the preformed cationic liposomes or alternatively encapsulated into the interior of the liposome, and that the resulting targeted cationic immunoliposomes are used to transfer DNA to tumor cells *in vivo* by direct intra-tumor injection or *in vitro* into freshly explanted tumor cells; (2) Yu *et al* teach that cationic liposome-mediated E1A (*i.e.*, a tumor suppressor) gene (DNA) transfer significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice and the ratio of DNA to liposome (ug: nmol) that is used, and teach attaching an anti-Her2/neu-encoded-p185-receptor antibody to said liposome prior to mixing with DNA in order to target to Her-2/neu expressing tumor cells; (3) US 6,448,390 discloses that cationic liposomes, such as for instance those comprising DOTAP/DOPE/DOPC and further comprising MPB-PE can be directly conjugated to thiolated proteins via a sulfur atom which was part of a sulfhydryl group at the carboxy-terminus of the protein prior to said conjugation; (4) US 2001/0008759 A1 discloses anti-Her2/neu scFv-cys antibody fragments conjugated to liposomes containing chemotherapeutic agents for treating cancer, the cysteine being a sulfhydryl containing group at the carboxy-terminus of the protein, the scFv-cys-targeted liposome being more effective than untargeted liposomes; (5) Morishige *et al* teach a coupling ratio of ug of antibody with a free SH group at the carboxy-terminus (part of Cys) to use per umol of lipid when conjugating Fab' antibody fragments with liposomes containing MPB-PE; (6) OSA was aware of the molecular weights of Fab' vs scFV fragments; (7) Wright and Huang teach attachment of thiolated antibody to preformed liposomes containing MPB-PE, and that such method facilitates proper orientation of the antibody and avoids the use of detergent that is employed with acylated antibody.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 1/25/08 on pages 7-20.

However, instant claim 73 does not recite ratio ranges and does not depend upon instant claim 1 that does recite ranges, therefore Applicant's arguments thereto are off point. In response to Applicant's argument that none of the cited references provides an enabling disclosure for direct conjugation of scFvs to cationic liposomes, Applicant is arguing the references separately. First, Yu *et al* teach making cationic liposomes that can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor, contrary to

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Applicant's assertion to the contrary. Applicant's argument that Yu *et al* teach "the ligand for the HER-2/neu encoded p185 receptor was not available" is a mischaracterization. Yu *et al* teach "...designing liposomes that can target the E1A gene to tumors that over-express p185 by incorporating into liposomes anti-p185 antibodies or the ligand for the HER-2/neu-encoded receptor (when it becomes available)", clearly indicating that anti-p185 antibodies were known and available, but the ligand for the HER-2/neu-encoded p185 receptor was not available. In addition, it was routine in the art at the time the invention was made to produce antibodies. Second, US 2001/0008759 A1 (Marks) was cited for the teaching that scFv can be prepared with a C-terminal cysteine for conjugation to liposomes; US 2001/0008759 A1 is being argued separately by Applicant with regard to the liposomes in said reference (stealth liposomes containing PEG) because US 6,448,390 B1 (Albritton) discloses that cationic liposomes (such as recited in the instant claim) containing MPB-PE can be directly conjugated to thiolated proteins via a sulfur atom that was part of a sulfhydryl group at the carboxy terminus of the protein prior to conjugation, and further teach scFv antibodies. Also, Wright and Huang teach that antibody can be attached to liposomes containing MPB-PE and the advantage of doing so, and Morishige *et al* teach conjugating Fab' fragments with liposomes and ratios for doing so. With regard to Applicant's comments on US 6,448,390 B1 not teaching direct conjugation between the cationic liposome and an antibody fragment, the said reference does teach direct conjugation, *i.e.*, the reference teaches that proteins can be thiolated via SATA to cationic liposomes containing DNA and the resulting protein, an antibody, can be directly conjugated to a cationic liposome containing MPB-PE (for instance, Example 13). The Examiner has previously addressed Applicant's arguments as detailed in applicant's Reply of May 7, 2007 (in the non-final rejection mailed 7/26/07). Briefly, with regard to Applicant's copy of Li and Huang, not cited in the instant rejection, although Li and Huang discuss difficulty in tissue-specific gene delivery, the reference US 6,248,721 B1 that is cited in the instant rejection, discloses direct intra-tumoral injection of the targeted cationic liposome *in vivo* or *in vitro*. Although Li and Huang discuss that DNA is a large molecule with a large hydrodynamic diameter as compared with a chemotherapeutic drug and Applicant asserts that OSA would not have predicted that additional molecules such as antibodies or antibody fragments could be added to the liposomes, the reference US 6,248,721 B1 that is cited in the instant rejection discloses covalently attaching ligands or antibodies to the surface of the cationic liposome that will also further comprise a desired DNA. The Examiner has also previously addressed Applicant's arguments to Morishige and Fab' fragments. The Examiner maintains that Morishige *et al* teach a mg Fab' to umol of lipid ratio that can be converted to a w:w ratio and OSA was aware of the molecular mass difference in Fab' and scFv fragments and could have adjusted the ratio accordingly. Once again, no ratio is recited in the instant claim.

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7. Claims 1-4, 7, 8, 12, 69, 73 and 75-80 are objected to because of the following informalities: Base claim 1 and dependent claim 73 recite the limitation “part of a sulfhydryl group at a carboxy terminus on said antibody fragment” rather than ‘part of a sulfhydryl group at the carboxy terminus on said antibody fragment’ [Examiner emphasis].

Appropriate correction is required.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
Group 1640 / Technology Center 1600
April 10, 2008

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/G.R. Ewoldt/
Primary Examiner, Art Unit 1644